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Use of Platelet-Rich Plasma for the Improvement of Pain and Function in Rotator Cuff Tears:

A Systematic Review and Meta-analysis With Bias Assessment

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Abstract

Background: Many clinical trials have investigated the use of platelet-rich plasma (PRP) to treat rotator cuff–related abnormalities. Several meta-analyses have been published, but none have focused exclusively on level 1 randomized controlled trials.

Purpose: To assess the efficacy of PRP for rotator cuff–related abnormalities and evaluate how specific tendon involvement, the inclusion of leukocytes, and the use of gel/nongel formulations affect pain and functional outcomes.

Study Design: Systematic review and meta-analysis.

Methods: The literature was screened following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Baseline, short-term, and long-term data were extracted for the Constant score, University of California, Los Angeles (UCLA) score, visual analog scale (VAS) for pain, retear rate, Simple Shoulder Test (SST), and American Shoulder and Elbow Surgeons (ASES) score. The 100-point modified Coleman Methodology Score (CMS) was used to assess methodological quality. Funnel plots and the Egger test were used to screen for publication bias, and sensitivity analysis was performed to evaluate the effect of potential outliers.

Results: A total of 18 level 1 studies were included in this review, 17 (1116 patients) of which could be included in quantitative analysis. The mean modified CMS was 79.4 ± 10.39. The Constant scores of patients who received PRP were significantly better short term (weighted mean difference [WMD], 2.89 [95% CI, 0.89–4.90]; $P < .01$) and long term (WMD, 2.66 [95% CI, 1.13–4.19]; $P < .01$). The VAS scores were significantly improved short term (WMD, −0.45 [95% CI, −0.75 to −0.15]; $P < .01$). Sugaya grade IV and V retears in PRP-treated patients were

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significantly reduced long term (odds ratio [OR], 0.34 [95% CI, 0.20–0.57]; $P < .01$). In PRP-treated patients with multiple tendons torn, there were reduced odds of retears (OR, 0.28 [95% CI, 0.13–0.60]; $P < .01$). Patients who received leukocyte-rich PRP had significantly better Constant scores compared with the leukocyte-poor PRP group, but there was no difference in VAS scores. Patients receiving PRP gel reported higher Constant scores compared with the controls, whereas those receiving nongel PRP treatments did not, although there was no difference in VAS scores. Long-term odds of retears were decreased, regardless of leukocyte content (leukocyte-poor PRP: OR, 0.36 [95% CI, 0.16–0.82]; leukocyte-rich PRP: OR, 0.32 [95% CI, 0.16–0.65]; all $P < .05$) or usage of gel (nongel: OR, 0.42 [95% CI, 0.23–0.76]; gel: OR, 0.17 [95% CI, 0.05–0.51]; all $P < .01$).

Conclusion: Long-term retear rates were significantly decreased in patients with rotator cuff–related abnormalities who received PRP. Significant improvements in PRP-treated patients were noted for multiple functional outcomes, but none reached their respective minimal clinically important differences. Overall, our results suggest that PRP may positively affect clinical outcomes, but limited data, study heterogeneity, and poor methodological quality hinder firm conclusions.

Keywords

rotator cuff; tendinopathy; biologic healing enhancement; platelet-rich plasma; minimal clinically important difference; systematic review and meta-analysis

A rotator cuff injury is the most common shoulder disorder treated by orthopaedic surgeons, with more than 30% of patients older than 60 years experiencing some form of a rotator cuff injury.[7,65] The standard treatment for rotator cuff tears is surgical repair, but as many as 70% of repair sites rupture,[21] and the biochemical and mechanical properties of the repaired tendon never match those of the intact tendon.[47,56] The current therapeutic options include direct sutures, autografts, allografts, and permanent tendon prostheses.[77] However, direct sutures are often associated with high retear rates,[24] and both autografts and allografts[44] are accompanied by several disadvantages, including increased surgery time, limited donor tendon sources, and sacrificed function of the donated tendon.[77]

The poor self-repair capability of the tendon and the limitations of current surgical and injection-based interventions have led to increased interest in platelet-rich plasma (PRP). PRP is an autologous mixture produced by centrifugal separation of whole blood.[37] The therapeutic effects of PRP are often attributed to the concentrated anabolic agents that it contains[33]; however, the centrifugation process also concentrates potentially deleterious agents, and even among the potentially beneficial growth factors and cytokines, effects are often pleiotropic.[36]

A number of studies reviewing the clinical efficacy of PRP for rotator cuff injuries have been published, but results have been mixed, and questions remain.[1,68,72,79] One of the principal factors limiting our understanding of PRP and its clinical efficacy is heterogeneity. Even among the randomized controlled trials that have been published to date, disease severity, methodological quality, and treatment formulation vary widely.[8] Additionally, the minimal clinically important difference (MCID) is rarely discussed, despite the fact that studies may

find statistically significant relationships that do not have clinical importance to patients, clinicians, or policy makers.[50]

A certain degree of variability between different PRP preparations is unavoidable because PRP is prepared at "point of care."[74] While this variability does not preclude meaningful efficacy conclusions, it does pose additional challenges that have been largely overlooked in the literature to date. We still do not understand how clinical outcomes are affected by participant characteristics or how the PRP formulation affects efficacy. This meta-analysis assessed how factors such as specific rotator cuff tendon(s) torn, use of PRP gel, and inclusion of leukocytes affect functional outcomes and pain.

METHODS

Search Methods for the Identification of Studies

This study was performed in accordance with the 2009 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and the PRISMA of Individual Patient Data (PRISMA-IPD) statement.[43,60] Using PubMed, MEDLINE, and the Cochrane Library, a comprehensive search of the literature was carried out in December 2017 (Figure 1) for "PRP OR platelet-rich plasma AND rotator cuff" filtered by "human" and "randomized controlled trial." A repeat search was conducted in December 2018 and did not identify any new articles.

Two authors (X.C. and I.A.J.) independently screened studies for eligibility. The preliminary screen identified 26 articles for eligibility review. There were 8 articles that were excluded because they did not meet the inclusion criteria. No additional articles were identified after reviewing bibliographies, leaving 18 full-text articles for qualitative analysis. One study[80] was excluded from quantitative analysis because the authors were not able to provide usable data after being contacted. A total of 17 articles were included in quantitative analysis.

Inclusion Criteria

Full-length English-language articles that reported clinical outcomes were screened for inclusion. Only level 1 studies, as defined by the Oxford Centre for Evidence-Based Medicine,[48] were included. No studies were excluded based on follow-up time, although all but 2 studies followed patients clinically for at least 6 months. Blinding, severity of injury, number of tendons involved, PRP preparation methodology, and type of outcome measures used were recorded but not used as a basis for inclusion/exclusion.

Modified Coleman Methodology Score

To assess methodological quality, we used a modified version of the Coleman Methodology Score (CMS).[12,61] CMS values range from 0 to 100. The higher the score, the lower the probability that outcomes are caused by chance, biases, or confounding factors.[42] In brief, scores are based on 11 criteria and broken into 2 parts (Appendix Table A1, available in the online version of this article). Scoring criterion A3, "number of surgical procedures," was modified such that PRP application during or after rotator cuff repair was not counted as an additional procedure. Furthermore, 7 points instead of 0 points were given if >10% patients

underwent more than 1 surgical procedure, as long as additional procedures were well-described. These modifications prevented the artificial deflation of scores while maintaining the original aims of the scoring system, as the CMS was originally intended for the assessment of studies on patellar tendinopathy. Without modifications to accommodate a different surgical procedure, a full score of 10 would have been impossible because of the high frequency of adjunct procedures in rotator cuff repair. Two authors (X.C. and I.A.J.) independently reviewed the included articles before meeting to collectively determine the final CMS value (Appendix Table A2, available online).

Selection of Outcome Measures

To ensure that there were sufficient data for quantitative analysis, outcome measures were selected based on how frequently they were used in the included studies. Only outcomes that were reported in ≥4 studies were included in the meta-analysis. The only exception was the Sugaya grade, which was reported in 8 studies but was not analyzed because of its direct overlap with the retear rate.

Meta-analysis

The outcomes of the Constant-Murley (Constant) score, University of California, Los Angeles (UCLA) score, visual analog scale (VAS) for pain, retear rate, Simple Shoulder Test (SST), and American Shoulder and Elbow Surgeons (ASES) score were extracted and categorized as follows: baseline, short term (up to 6.5 months' follow-up), and long term (≥1-year follow-up, if available). When studies did not report a standard deviation, it was calculated from the standard error or 95% confidence interval (CI). The standard deviation calculated from the 95% CI used critical values from the *t* distribution because of the small sample size. The mean was calculated from the median and interquartile range, as suggested by Wan et al,[70] and the standard deviation was calculated using the Cochrane method.[25] VAS scores that were reported on a 0-to-100 scale[34] were converted to a 0-to-10 scale for consistency. Sugaya grades IV and V were considered a retear event.

The weighted mean differences (WMDs) with 95% CIs were calculated for the continuous outcomes for each study. Because each outcome of interest was assessed separately, and the unit of measurement was the same across studies for the specified outcomes, the mean difference was not standardized. When the outcome was binary, the odds ratio (OR), along with the 95% CI, was calculated and reported. If any of the 2 × 2 tables for a study had cell counts equal to zero ("zero cells"), a continuity correction of 0.5 was added to all cells for the study to be included. A random-effects model was used under the assumption that the true effect would not be the same across all the studies and because variability across studies for each outcome was expected.

A meta-analysis was performed by time subgroups (baseline, short term, and long term) and overall to determine the efficacy of PRP versus control. For each outcome, several variables of interest (blinding, injury severity, specific rotator cuff tendons torn/affected, leukocyte type, and gel formulation) were evaluated within each time point; however, if there were too few studies in a particular subgroup to be informative, that subgroup was not reported. The following covariates were excluded: injury severity, type of activating agent used (if any),

and study blinding. There were 3 subgroups that could be analyzed: rotator cuff tendons torn/affected, leukocyte-rich PRP (LR-PRP) versus leukocyte-poor PRP (LP-PRP), and use of gel versus injection. LR-PRP was defined as PRP having a white blood cell (WBC) concentration exceeding that of whole blood (4.0–10.0 per uL^3), while LP-PRP was defined as PRP having a lower WBC concentration than whole blood.[53] For studies that did not explicitly report the WBC concentration, the PRP preparation kit and associated manufacturer data were used to determine WBC content and categorize studies into respective LR-PRP and LP-PRP groups.

Forest plots were used to determine if there was variable-specific efficacy heterogeneity. The I^2 test was used to assess heterogeneity based on the thresholds reported in the Cochrane Handbook for Systematic Reviews of Interventions[25]: 0%–40% might not be important, 30%–60% may represent moderate heterogeneity, 50%–90% may represent substantial heterogeneity, and 75%–100% may represent considerable heterogeneity. Funnel plots and the Egger test were used to assess potential publication bias. Sensitivity analysis was performed to evaluate the effect of potential outliers. For retears, this was done by removing studies that reported zero events one at a time. All analyses were performed using STATA version 15.1 (StataCorp).

Clinical Interpretation

The MCID was used to evaluate the potential clinical importance of reported findings. A 10% difference threshold was considered based on the rationale outlined in the American Academy of Orthopaedic Surgeons (AAOS) evidence-based guidelines and published anchor-based values.[28] However, given the controversial nature of the AAOS guidelines and apparent disconnect between the AAOS recommendations and what occurs in clinical practice,[32] differences were only considered clinically insignificant when they fell below half of the MCID used by the AAOS (ie, <5% difference), which is conservative with respect to MCID values reported in the literature for rotator cuff patient-reported outcome (PRO) measures (Table 1).

RESULTS

A total of 18 level 1 studies were included in this review (Table 2). None of the published works included overlapping participant groups. The majority of studies compared surgical repair using PRP to repair without additional treatment in middle-aged patients with full-thickness tears. There was extensive heterogeneity between the types of treatments that were administered and the way in which they were characterized (Appendix Table A3, available online). For example, 6 different activating agents and 12 different kits were used to prepare the PRP treatments. There was wide variability between the total PRP volume that was administered (range, 0.4–20 mL), and about a third of the studies failed to report the PRP volume altogether. Only a handful of studies reported platelet or leukocyte concentration. There was also variability in the degree of injury. There were 4 studies that did not report which rotator cuff tendons were affected, 8 studies only included participants who had injuries exclusively to the supraspinatus, and 6 studies included participants with multiple tendons affected.

Methodological Quality

The mean modified CMS score was 79.4 ± 10.39. Less than half of the studies scored full points for sample size (>60 patients required), which limits their individual clinical relevance.[2] Additionally, no studies followed participants for longer than 24 months.

Overview of Meta-analysis

Of the 18 (1151 patients) studies included in this review, 17 (1116 patients) contained analyzable data and were included in the meta-analysis. Of the 1116 patients with available data, 545 were treated with PRP. The following outcome measures were used (Table 3): Constant score (10 studies), UCLA score (6 studies), VAS (10 studies), retear rate (11 studies), ASES score (4 studies), and SST (4 studies). Moreover, 3 authors were contacted for additional data; 2 did not respond,[30,80] and 1 author[73] was not able to provide the data requested.

Patients who received PRP reported improvement in the Constant score at short term (WMD, 2.89 [95% CI, 0.89–4.90]; $P < .01$), long term (WMD, 2.66 [95% CI, 1.13–4.19]; $P < .01$), and overall (WMD, 1.80 [95% CI, 0.63–2.96]; $P < .01$) (Appendix Figure A1, available online). For the VAS, improved scores were reported in PRP-treated patients at short term (WMD, −0.45 [95% CI, −0.75 to −0.15]; $P < .01$) and overall (WMD, −0.27 [95% CI, −0.51 to −0.04]; $P = .02$) (Appendix Figure A2, available online). For the ASES score, there was no significant difference between the PRP- and non–PRP treated patients at any time points (Appendix Figure A3, available online). There were reduced odds of Sugaya grade IV and V retears in PRP-treated patients compared with non–PRP treated patients at long term (OR, 0.34 [95% CI, 0.20–0.57]; $P < .01$) and overall (OR, 0.42 [95% CI, 0.26–0.67]; $P < .01$) (Appendix Figure A4, available online). Patients who received PRP treatment reported higher UCLA scores at short term (WMD, 1.75 [95% CI, 0.85–2.64]; $P < .01$), long term (WMD, 1.39 [95% CI, 0.35–2.43]; $P < .01$), and overall (WMD, 0.97 [95% CI, 0.23–1.70]; $P = .01$) (Appendix Figure A5, available online). For the SST, patients who received PRP treatment reported better scores at long term (WMD, 0.41 [95% CI, 0.09–0.73]; $P = .01$). Moderate to substantial heterogeneity was reported at baseline ($I^2 = 68.6\%$; $P < .01$) and overall ($I^2 = 55.7\%$; $P < .01$) for the Constant score; overall ($I^2 = 68.5\%$; $P < .01$) for the UCLA score; baseline ($I^2 = 50.9\%$; $P = .03$), long term ($I^2 = 87.5\%$; $P < .01$), and overall ($I^2 = 82.4\%$; $P < .01$) for the VAS; and short term ($I^2 = 71.6\%$; $P = .03$) for the ASES score. Significant heterogeneity was not observed for the SST (all $P > .05$).

Meta-analysis of Covariates

The following 3 categories were selected for in-depth analysis: the specific rotator cuff tendons involved (Figure 2), the use of LR-PRP/LP-PRP (Figure 3), and the use of gel/nongel PRP (Figure 4). Additionally, sufficient data for meaningful comparisons were only available for the Constant score, VAS, and retear rate.

For the long-term Constant score, it appeared that scores did not differ between the PRP and control groups when PRP was used to treat supraspinatus tears exclusively (Figure 2A). However, patients who received PRP treatment reported better Constant scores compared with the control if multiple tendons were torn (WMD, 4.87 [95% CI, 2.89–6.85]; $P < .01$).

PRP treatment did not appear to cause significant changes in VAS scores for any of the rotator cuff tendon subgroups (Figure 2B). Although more data are needed to determine if there really was no difference between treatment groups for long-term retear outcomes in supraspinatus tears, it appeared that PRP treatment reduced the odds of retears in patients with multiple tendon tears compared with the control (OR,0.28 [95% CI, 0.13–0.60]; $P < .01$) (Figure 2C). No significant heterogeneity was reported in the multiple tendon subgroup for the Constant score or retear rate at long-term follow-up (all $P > .05$), although there was substantial heterogeneity among the nonspecified group ($I^2 = 70.7\%$; $P = .03$) for the VAS.

Among studies in which leukocyte inclusion or exclusion was reported, patients who received LR-PRP had improved Constant scores (WMD, 3.19 [95% CI, 1.44–4.95]; $P < .01$) (Figure 3A). There was no significant difference between treatment groups, regardless of leukocyte content, for VAS scores (Figure 3B). The odds of retears at long term were reduced if the patient received PRP, regardless of leukocyte inclusion (LP-PRP: OR, 0.36 [95% CI, 0.16–0.82]; LR-PRP: OR, 0.32 [95% CI, 0.16–0.65]; all $P < .05$) (Figure 3C). There was substantial heterogeneity reported for the LP-PRP group for the Constant score ($I^2 = 69.6\%$; $P = .04$) and for the LR-PRP group ($I^2 = 83.6\%$; $P < .01$) for the VAS. There was no significant heterogeneity for either subgroup for the retear rate at long-term follow-up (all $P > .05$).

The long-term Constant scores of participants who received nongel PRP treatment were not significantly different from those in the comparator groups (Figure 4A); however, patients who received PRP gel reported higher Constant scores than those in their respective comparison groups (WMD, 3.81 [95% CI, 1.62–6.00]; $P < .01$). For the VAS, the PRP and control groups did not differ, although there was substantial heterogeneity in the nongel subgroup ($I^2 = 90.1\%$; $P < .01$) (Figure 4B). At long-term follow-up, PRP reduced the odds of retears in both the nongel (OR, 0.42 [95% CI, 0.23–0.76]; $P < .01$) and gel (OR, 0.17 [95% CI, 0.05–0.51]; $P < .01$) groups (Figure 4C).

While statistically significant differences were observed for several PROs, the improvements compared with control treatments were less than even the most conservative anchor-based estimates of the MCID for shoulder injuries within the literature. None of the overall, short-term, or long-term effect sizes reached 5% of the absolute difference threshold used to approximate the MCID. In the short term, the Constant score reached 57.8% of the MCID, while the VAS, ASES score, and SST reached 90.0%, 40.8%, and 75.0%, respectively. In the long term, the Constant score reached 53.2% of the MCID, while the VAS, ASES score, and SST reached 68.0%, 26.6%, and 68.3%, respectively. Overall, the Constant score reached 36.0% of the MCID, while the VAS, ASES score, and SST reached 54.0%,14.8%, and 38.3%, respectively.

Publication bias was assessed using funnel plots (Figure 5, A–C; Appendix Figures A7–A9, available online). The plots for all outcomes, with the exception of the Constant score, appeared to be asymmetric, with some missingness at the lower portion of each respective plot, suggesting possible publication bias. The funnel plots for the Constant score, UCLA score, and VAS appeared to have some outliers. The outliers were not attributed to any of the

subgroups in particular. When the Egger test was performed, there was indication of small study effects for the UCLA score and VAS ($P < .05$) most likely because of heterogeneity and small sample bias.

Sensitivity analysis was performed by removing potential outliers reported in the funnel plots one by one. For the UCLA score, the short- and long-term subgroups became nonsignificant when the Pandey et al[49] study was removed. For the VAS, removing the studies by Rha et al[52] or Pandey et al[49] made the short-term results no longer significant. However, removing the Zhang et al[78] study made the long-term subgroup significant (WMD, −0.47 [95% CI, −0.84 to −0.11]; $P = .01$). For the SST, removing the potential outlier (study of Gumina et al[22]) made the long-term results no longer significant (WMD, 0.43 [95% CI, −0.10 to 0.96]; $P = .11$), whereas overall results became significant (WMD, 0.43 [95% CI, 0.02 to 0.83]; $P = .04$). Removing other potential outliers for these and other outcome measures did not change the results for the time subgroups or overall. Removing articles that reported zero cells for the retear outcome did not change the time subgroups or overall results. None of the studies reporting potential outliers or zero cells were removed from final analysis, as there was no indication of errors in the data reported.

DISCUSSION

Other recent meta-analyses investigating the effect of PRP on rotator cuff pain and function have drawn inconsistent conclusions. Cai et al[4] found no difference in clinical outcome scores (Constant, UCLA, ASES, and SST) between PRP and control groups but still concluded that PRP may improve tendon-to-bone healing based on significant differences in the failure-to-heal rate. Hurley et al[27] found that the use of PRP increased tendon healing and improved Constant, VAS, and UCLA scores and concluded that PRP improves pain, function, and the healing rate. Our meta-analysis of 17 level 1 randomized controlled trials (1116 unique patients) found statistically significant decreased pain in patients treated with PRP. PRP was found to improve Constant and VAS scores (similar to Hurley et al) but not ASES scores (similar to Cai et al).

Statistical significance may not necessarily translate to clinical significance. None of the functional outcomes included in this study reached their respective MCIDs, suggesting that making conclusions based on statistical significance alone may be erroneous and misleading. This study is the first level 1 review to provide additional clinical context to quantitative results through the MCID, suggesting that PRP may not necessarily be better than placebo for the treatment of rotator cuff injuries.

Among functional outcomes, results varied based on the tendons injured, leukocyte inclusion in the PRP formulation, and whether PRP was applied as a gel. While there are no tendon-specific results in the literature to compare with this study's data, there have been subgroup analyses on leukocyte inclusion and type of PRP application. A meta-analysis by Warth et al[72] found no statistically significant difference in Constant scores and retear rates of patients undergoing rotator cuff repair with a PRP liquid injection versus gel. In contrast, this study showed that the use of PRP gel was associated with increased Constant scores. Nongel applications did not show improvement over the control at long term, although both

types were associated with a decreased retear rate. Potential explanations for this difference comprise the inclusion of level 2 studies by Warth et al and a larger data set used in this study. Despite the differences observed in this study, no recommendation can be made on the ideal PRP type, as there is still a scarcity of high-quality randomized controlled trials comparing PRP gel with PRP liquid.

LR-PRP was found to increase Constant scores, and both LR-PRP and LP-PRP decreased retear rates in the long term compared with the control. These findings differ from the results of a meta-analysis by Fitzpatrick et al,[18] which found significant pain reduction (as measured by the VAS) in patients treated with LR-PRP compared with LP-PRP. This discrepancy could be because Fitzpatrick et al analyzed multiple different tendinopathies and specifically excluded studies that involved surgical interventions, such as full-thickness rotator cuff tears. There is a shortage of studies investigating the role of leukocytes in PRP's efficacy, with many clinical trials failing to report the leukocyte content. Additional studies are needed before conclusions for LR-PRP can be drawn.

PRP appeared to significantly reduce the retear rate compared with the control. This reduction in the retear rate was independent of the gel/liquid application method or leukocyte inclusion. Of interest, PRP was found to reduce long-term retear rates in patients with multiple rotator cuff tendons torn. Prior meta-analyses have reported conflicting results on the retear rate, with several[72] reporting no significant difference between PRP-treated and control groups and others[68] finding significantly reduced retear rates in PRP-treated patients. Vavken et al[68] concluded that PRP treatment for the prevention of rotator cuff retears is not cost-effective, despite reduced retear rates caused by an incremental cost-effectiveness ratio of $127,893 per quality-adjusted life-year gained. Reduction in the retear rate remains a difficult metric to compare between studies because of study heterogeneity, and no MCID exists for the retear rate because any retear is considered clinically significant. The reduced retear rates observed in this study are promising and may support the use of PRP for decreasing retears, although more studies are needed to clarify the role of PRP in long-term rotator cuff healing.

The MCID for each PRO measure was approximated using half of a recommended 10% threshold (5%). While multiple PRO measures were shown to have statistically significant improvements in this study, PRO measures at all analyzed time points failed to reach the 5% absolute difference threshold, with only the short-term VAS effect size rising above 4%. Moreover, compared with the MCID values in the literature, none of the short-term, long-term, or overall effect sizes reached their respective average MCID.

The MCID is not without limitations. First, MCIDs reported in other rotator cuff studies have varying degrees of credibility, as several studies did not quantify data distribution via standard deviations, standard errors, or confidence intervals. Additionally, there is no guideline on a specific percentage difference that accurately approximates the MCID for the rotator cuff. A 10% difference benchmark from the AAOS guidelines for the usage of MCIDs in knee osteoarthritis was initially considered. However, the MCID is not a universal fixed attribute that can be transferred across patient populations and all diseases,[16,76] but it has been shown that as the pooled estimate falls below half of the MCID, it becomes

progressively less likely that an appreciable number of patients will achieve important benefits from treatment.[31] As such, we adopted a 5% absolute difference threshold for the MCID in this study. To further address the issues of MCID heterogeneity and comparability, anchor-based MCIDs in the literature were collected. These median, mean, maximum, and minimum MCID values are presented to further support the conservative nature of the 5% threshold adopted in this study.

This study suggests that PRP may not provide clinically meaningful improvements in pain or function, despite statistically significant findings. However, this does not mean that the statistical improvements demonstrated in this meta-analysis should be disregarded. PRP composition tends to be highly variable, and the literature as a whole may not accurately represent the efficacy of individual treatments. A side-by-side comparison of 6 systems demonstrated similar platelet concentration and capture efficiency,[14] but there were significant differences in WBCs, neutrophils, red blood cell concentration, and pH. Other variables that may significantly influence PRP efficacy include the use of activation, platelet count, quantification of additional growth factors (EGF, FGF, PDGF, VEGF, TGF-beta), and timing of PRP administration.[55] Each of these factors presents additional sources of variability that hinder the interpretation of PRP trials. Moreover, as mentioned previously, a reduction in the retear rate was observed, which can be considered clinically significant.

A limitation of this review is that it includes both traumatic injuries and tendon abnormalities more generally. While tendinopathy has been shown to precede tearing,[69] there are important biological differences between the two that likely have clinical implications. Tendinopathy is a debilitating injury initiated by a number of biological and physical factors, including age, oxidative stress, and loading. In contrast to partial or complete tendon ruptures, a histological examination shows that tendinopathy results in disordered healing without macroscopic tearing or inflammation.[47,57,58]

The quantitative results of this study are limited by several factors. Study heterogeneity and a small number of studies within subgroups are major limitations. There is extensive variability in the PRP kits that were used, PRP formulation, outcome usage, and data reporting. Nearly every study included in this review used a different PRP kit, each of which utilized different preparation protocols that changed the final composition of PRP delivered. Gel formulations were used in only 3 studies. While there was relative homogeneity in the usage of nongel PRP, the limited number of studies on PRP gel precludes meaningful comparisons between formulations. The injection technique itself was also variable, as some studies used intratendinous injections, whereas others used subacromial injections. Variable outcome usage by different studies is another limitation. For example, SST and ASES scores were reported by few studies, leading to lower power statistical analyses. Additionally, variable data reporting limited the comparability of studies. Furthermore, 12 of the 17 included studies did not report leukocyte concentration, and 4 studies did not report which rotator cuff tendons were affected in their study cohorts. There was also high variability in the usage of PRP activation, temperature, and timing and volume of injections, which may change the biological activity and yield of PRP.[15] The poor reporting and heterogeneity of these variables have been widely cited[8,45] and limit interstudy comparability.

An additional limitation specific to comparing rotator cuff studies is the variability in adjunct procedures. Biceps tenodesis and acromioplasty, for example, are 2 procedures that are often performed alongside rotator cuff repair because of the high association of rotator cuff tears with bicipital tendinitis[46] and degenerative arthritic changes at the head of the clavicle.[11] The high frequency of additional procedures makes it difficult to compare patients within and between different studies. Procedural heterogeneity may ultimately be unavoidable, although larger scale trials may partially mitigate this limitation by providing more robust data sets to work with.

Another possible confounding factor is the repair technique (single- vs double-row repair), although the literature as a whole suggests no relationship between most PRO scores and the type of repair. For instance, a 2014 meta-analysis[41] showed that while rotator cuff tears treated with single-row repair had significantly higher retear rates than those treated with double-row repair, there were no significant differences in PRO scores. A more recent meta-analysis by Hantes et al[23] also found no significant differences in outcome scores between the 2 techniques, although double-row repair was found to have a significantly higher tendon healing rate. In the same study, patients with healed tendons reported higher UCLA and Constant scores than those with retorn tendons, suggesting that double-row repair may actually improve the likelihood of higher outcome scores in the long term because of its association with superior tendon healing and fewer retears compared with single-row repair. Ultimately, the influence of repair technique on the patients analyzed within this study is unclear and may partially explain the finding of decreased retear rates in PRP-treated patients.

CONCLUSION

The strength of this study is that it reviewed exclusively level 1 randomized controlled trials, analyzed multiple subgroups, and compared quantitative results with the MCID. This study also attempted to quantify the effects of using LR-PRP versus LP-PRP, gel versus nongel preparations, and tendon-specific outcomes, although there were insufficient data to make definitive conclusions in these subdomains. One notable finding was that long-term retear rates significantly decreased in groups treated with PRP, but further investigation into the cost-effectiveness of PRP in rotator cuff healing is needed. Several PRO measures (Constant score, VAS, retear rate) were significantly improved in PRP-treated patients, but all PROs failed to reach the 5% MCID threshold. More data are needed from well-designed, appropriately powered clinical trials on the use of PRP for rotator cuff abnormalities. Given the wide disparity between the MCID and effect sizes of the PRO measures included in this study, we can neither recommend nor discourage the use of PRP for rotator cuff injuries, despite finding statistically significant improvements in pain and function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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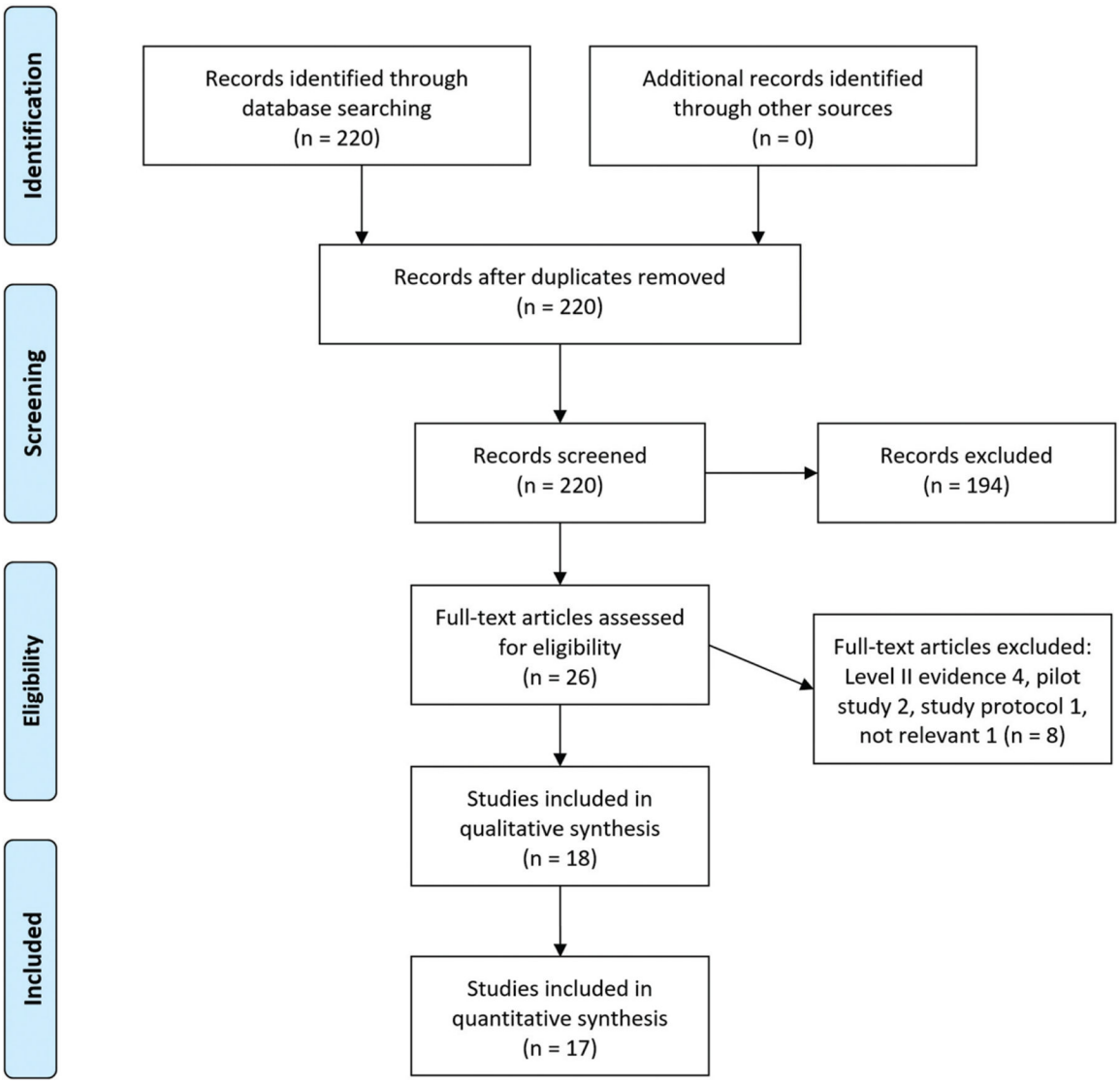

Figure 1.

Flow diagram based on the PRISMA (Preferred Reporting Items for Systematic Meta-Analyses) guidelines outlining the literature search, screening, review, and inclusion.

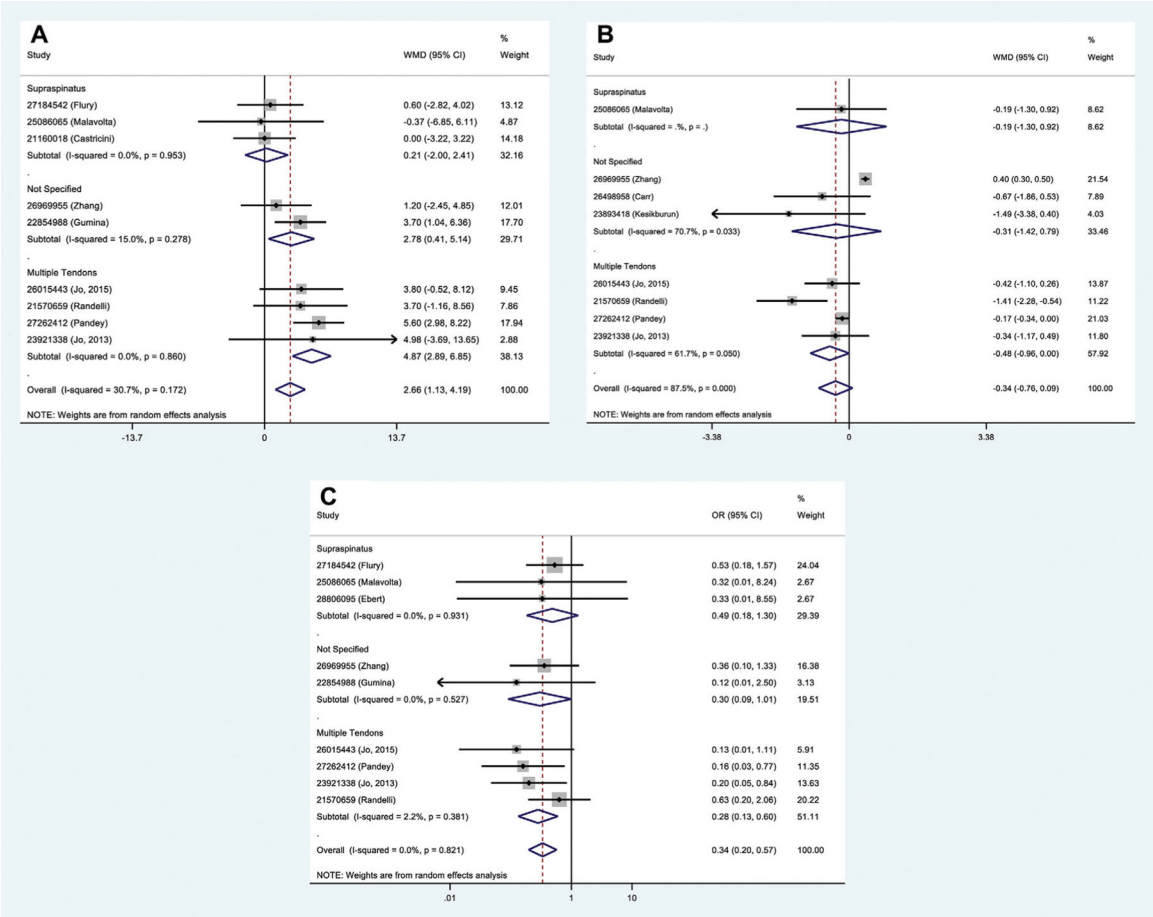

Figure 2.

Clinical outcomes based on tendon(s) affected at long-term follow-up: (A) Constant score, (B) visual analog scale, and (C) retear rate. OR, odds ratio; WMD, weighted mean difference.

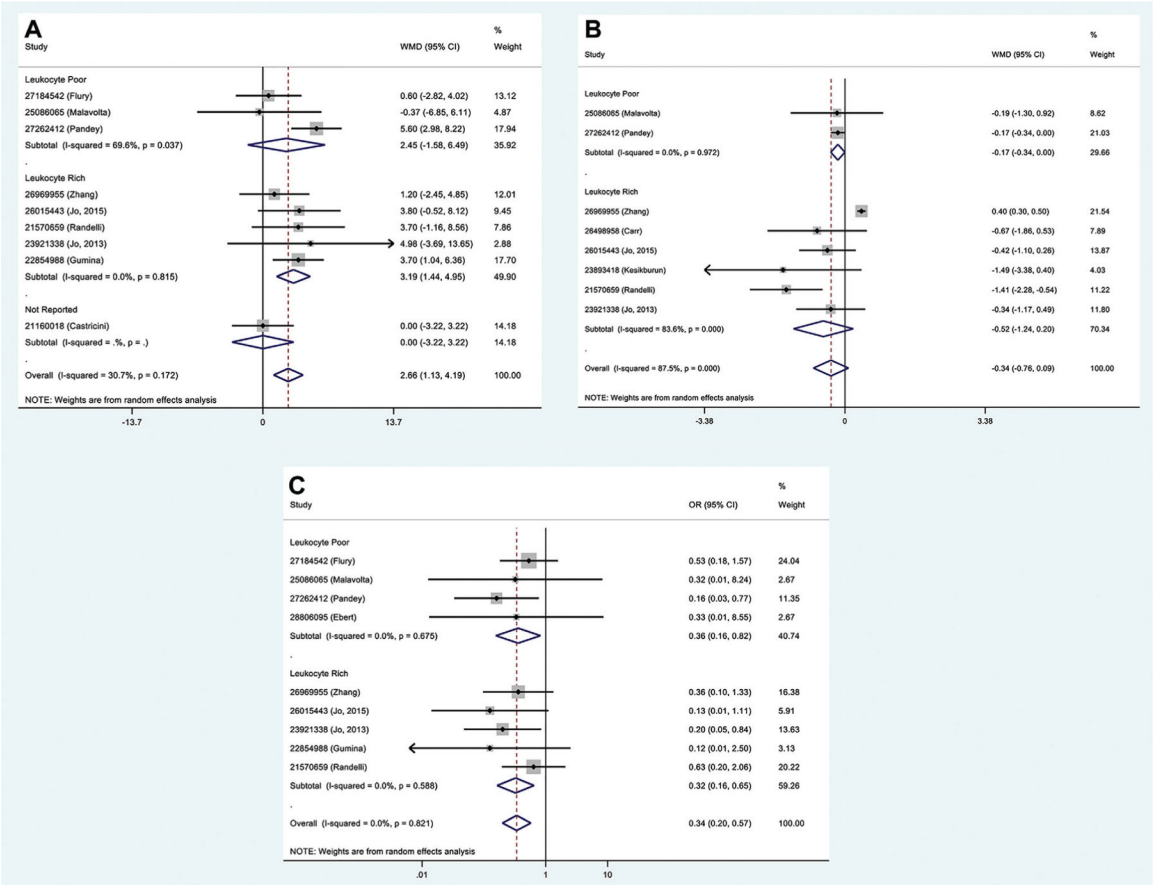

Figure 3.

Clinical outcomes based on the use of leukocyte-rich versus leukocyte-poor platelet-rich plasma at long-term follow-up: (A) Constant score, (B) visual analog scale, and (C) retear rate. OR, odds ratio; WMD, weighted mean difference.

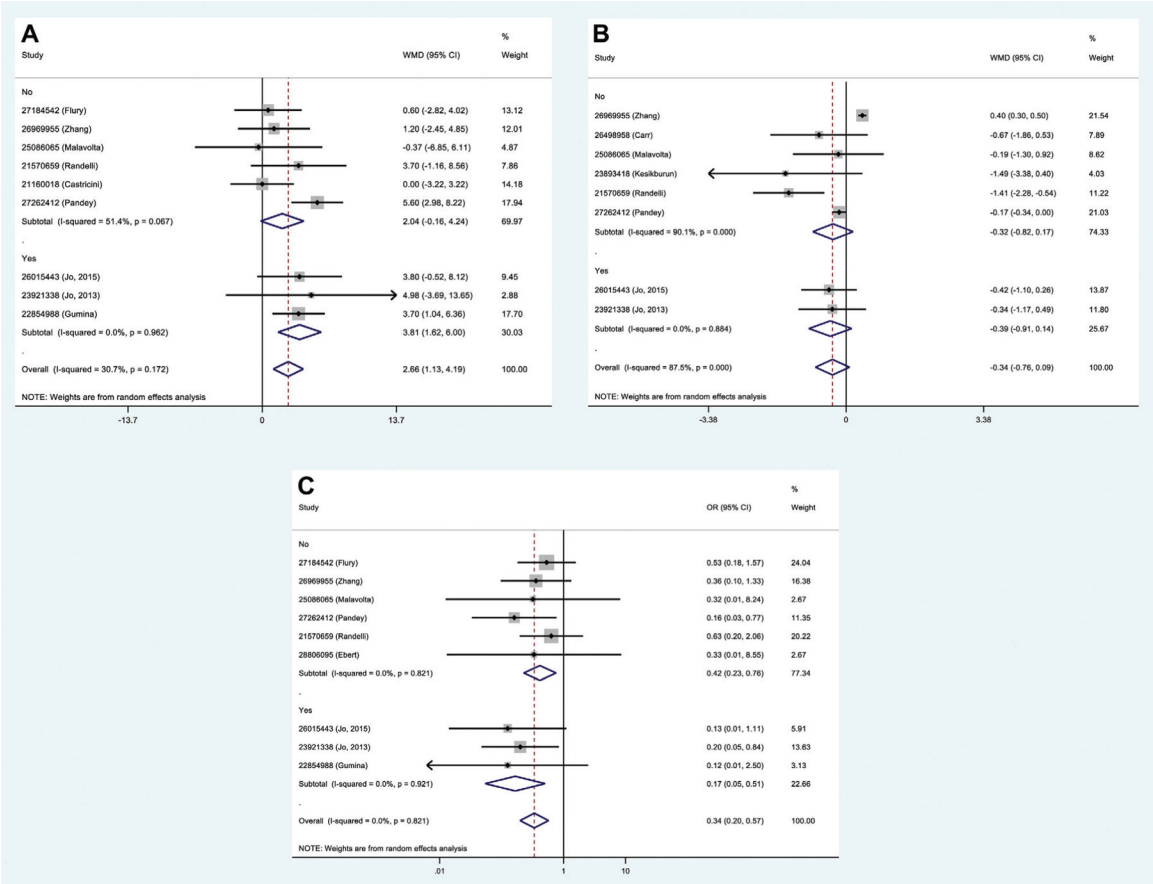

Figure 4.

Clinical outcomes based on the use of gel application at long-term follow-up: (A) Constant score, (B) visual analog scale, and (C) retear rate. OR, odds ratio; WMD, weighted mean difference.

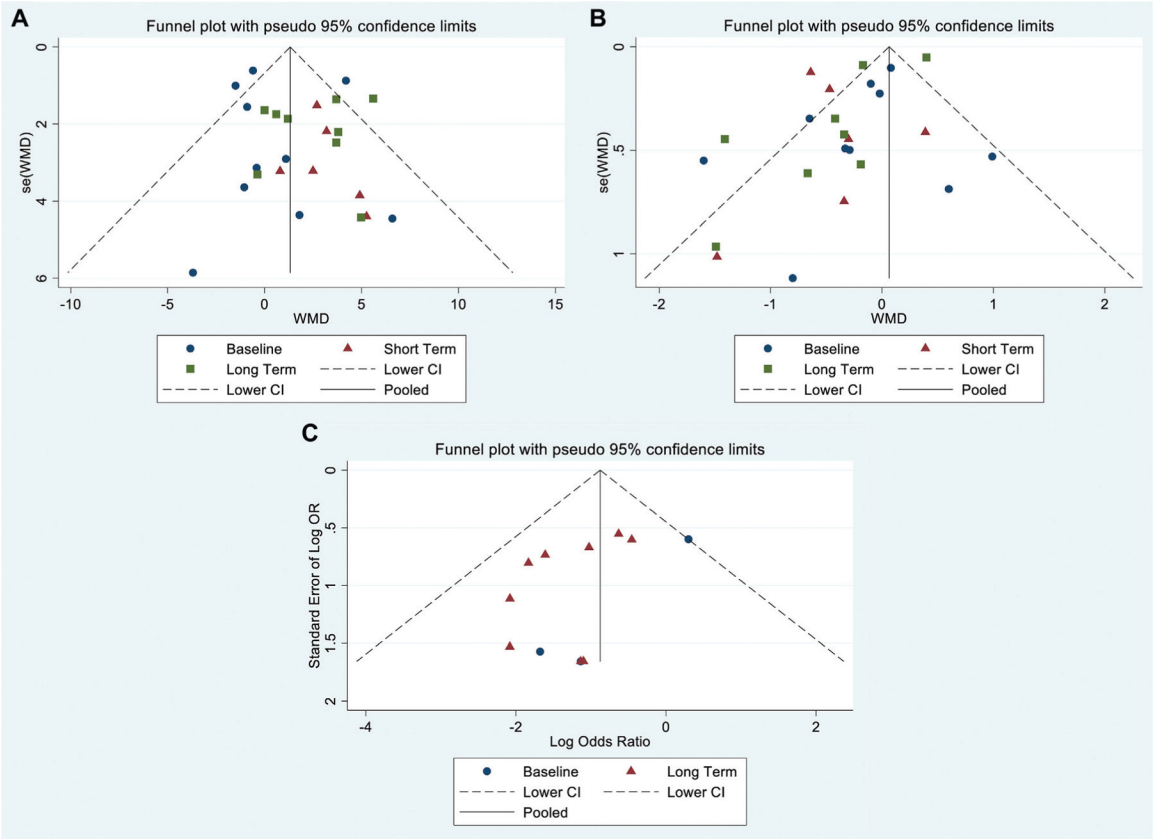

Figure 5.

Funnel plots for clinical outcomes: (A) Constant score, (B) visual analog scale, and (C) retear rate. OR, odds ratio; WMD, weighted mean difference.

TABLE 1

Overview of MCID Compared With WMD[a]

Patient-Reported Outcome Measure	WMD (95% CI)	MCID Calculated From 5% Difference	Minimum MCID	Maximum MCID	Median MCID	Mean MCID	% of Mean MCID
Constant	1.80 (0.63 to 2.96)	5.00	5.70	17.00	10.70	11.45	16.16
VAS	−0.27 (−0.51 to −0.04)	0.50	0.80	2.75	1.40	1.58	17.05
ASES	0.74 (−0.77 to 2.24)	5.00	6.40	21.90	15.16	15.50	4.77
SST	0.23 (−0.07 to 0.53)	0.60	1.50	2.40	2.27	2.11	10.91

[a]Studies reporting the minimal clinically important difference (MCID) were found using a comprehensive literature search. Only articles using anchor-based methods were used as benchmarks in this study because alternative MCID derivations such as distribution-based methods may not be as accurate in assessing improvements from the patient's perspective. The weighted mean difference (WMD) column displays the overall effect sizes found in this meta-analysis. The following columns show the MCID calculated from a 5% difference for each outcome measure and the minimum, maximum, and mean MCID values found within the literature (American Shoulder and Elbow Surgeons [ASES] score,[20,40,59,62,64,75] visual analog scale [VAS],[10,38,59,63,64] Constant score,[9,10,26,35,59,66] and Simple Shoulder Test [SST][59,62,64,67]). "% of mean MCID" was obtained by dividing the WMD by the mean MCID. The retear rate was not included because there is no MCID, as any retear is considered clinically significant. The University of California, Los Angeles (UCLA) score was also excluded, as the scoring system cannot be used to determine improvements from baseline because it contains a question on "satisfaction of patient."

TABLE 2

Overview of Studies

First Author (Year)	Comparator	Type of Injury	Specific Rotator Cuff Tendons Torn/Affected	Country	Mean Age, y	Male Patients, n	Female Patients, n
Ebert et al[17] (2017)	Repair without treatment	Full-thickness tear	Supraspinatus only	Australia	60	28	25
D'Ambrosi et al[13] (2016)	Repair without treatment	Full-thickness tear	Supraspinatus only	Italy	60	19	21
Flury et al[19] (2016)	Ropivacaine	Full-thickness tear	Supraspinatus only	Switzerland	58	38	82
Zhang et al[78] (2016)	Repair without treatment	Full-thickness tear	Not specified	China	57	31	29
Pandey et al[49] (2016)	Repair without treatment	Full-thickness tear	Supraspinatus or infraspinatus	India	54	74	28
Zumstein et al[80] (2016)[a]	Repair without treatment	Full-thickness tear	Supraspinatus and/or infraspinatus	France	66	18	17
Carr et al[5] (2015)	Repair without treatment	Full-thickness tear	Not specified	UK	54	27	33
Jo et al[30] (2015)	Repair without treatment	Subacromial impingement or partial-thickness tear	Supraspinatus and/or infraspinatus and/or subscapularis (average, 1.7 tendons)	Republic of Korea	61	27	57
Wang et al[71] (2015)	Repair without treatment	Full-thickness tear	Supraspinatus only	Australia	59	28	32
Malavolta et al[39] (2014)	Repair without treatment	Full-thickness tear	Supraspinatus only	Brazil	55	17	37
Kesikburun et al[34] (2013)	Saline	Tendinosis or partial-thickness tear	Not specified	Turkey	53	13	27
Weber et al[73] (2013)	Repair without treatment	Full-thickness tear	Not specified	USA	62	36	24
Rha et al[52] (2013)	Dry needling	Tendinosis or partial-thickness tear	Supraspinatus only	Republic of Korea	53	17	22
Jo et al[29] (2013)	Repair without treatment	Full-thickness tear	Supraspinatus and/or infraspinatus and/or subscapularis (average, 2.3 tendons)	Republic of Korea	63	24	24
Ruiz-Moneo et al[54] (2013)	Repair without treatment	Full-thickness tear	Supraspinatus and/or infraspinatus	Spain	56	30	39
Gumina et al[22] (2012)	Repair without treatment	Full-thickness tear	Supraspinatus only	Italy	61	41	35
Randelli et al[51] (2011)	Repair without treatment	Full-thickness tear	Supraspinatus and/or infraspinatus and/or subscapularis (average, 1.8 tendons)	Italy	61	21	42
Castricini et al[6] (2011)	Repair without treatment	Full-thickness tear	Supraspinatus only	Italy	55	40	48

[a]This study was not included in the meta-analysis because of the inability of the authors to provide data.

TABLE 3

Meta-analysis Comparisons by Time for Multiple Clinical Outcome Measures[a]

Time Point	No. of Studies[b]	No. of Participants	Statistical Method	Effect Size
Constant				
Overall	25 (10)	1781	WMD (95% CI)	1.80 (0.63 to 2.96)
Baseline	10	720		0.51 (−1.46 to 2.48)
Short term	6	413		2.89 (0.89 to 4.90)
Long term	9	648		2.66 (1.13 to 4.19)
UCLA				
Overall	16(6)	1056	WMD (95% CI)	0.97 (0.23 to 1.70)
Baseline	6	394		0.11 (−0.42 to 0.64)
Short term	4	276		1.75 (0.85 to 2.64)
Long term	6	386		1.39 (0.35 to 2.43)
VAS				
Overall	24 (10)	1408	WMD (95% CI)	−0.27 (−0.51 to −0.04)
Baseline	10	579		−0.14 (−0.43 to 0.16)
Short term	6	360		−0.45 (−0.75 to −0.15)
Long term	8	469		−0.34 (−0.76 to 0.09)
ASES				
Overall	11(4)	949	WMD (95% CD)	0.74 (−0.77 to 2.24)
Baseline	4	343		0.71 (−3.27 to 4.68)
Short term	3	278		2.04 (−4.25 to 8.32)
Long term	4	328		1.33 (−0.12 to 2.78)
SST				
Overall	10(4)	609	WMD (95% CD)	0.23 (−0.07 to 0.53)
Baseline	4	255		0.02 (−0.72 to 0.75)
Short term	2	111		0.45 (−0.40 to 1.31)
Long term	4	243		0.41 (0.09 to 0.73)

Time Point	No. of Studies[b]	Treatment Events, n[c]	Control Events, n	Statistical Method	Effect Size
Retear rate					

Time Point	No. of Studies[b]	Treatment Events, n[c]	Control Events, n	Statistical Method	Effect Size
Overall	12 (11)	36/384	73/377	Odds ratio (95% CI)	0.42 (0.26 to 0.67)
Short term	3	10/85	10/81		0.93 (0.33 to 2.63)
Long term	9	26/299	63/296		0.34 (0.20 to 0.57)

[a]ASES, American Shoulder and Elbow Surgeons; SST, Simple Shoulder Test; UCLA, University of California, Los Angeles; VAS, visual analog scale; WMD, weighted mean difference.

[b]Numbers in parentheses signify how many individual studies reported that specific clinical outcome measure; this differs from the total number of studies, which double counts the studies that report both short-term and long-term outcomes.

[c]For each column, the numerator refers to the number of events (retears) and the denominator refers to the total number of participants in the treatment and control groups, respectively.